

# Oseltamivir and Risk of Lower Respiratory Tract Complications in Patients With Flu Symptoms: A Meta-analysis of Eleven Randomized Clinical Trials

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**An independent reanalysis of 11 randomized clinical trials shows that oseltamivir treatment reduces the risk of lower respiratory tract complications requiring antibiotic treatment by 28% overall (95% confidence interval [CI], 11%–42%) and by 37% among patients with confirmed influenza infections (95% CI, 18%–52%).**

In a pooled analysis of 10 randomized clinical trials, Kaiser et al [1] concluded that oseltamivir reduced the risk of influenza-related lower respiratory tract complications (LRTCs) requiring antibiotic therapy by 55%, from 10.3% to 4.6%. All 10 trials had been funded by Roche, the manufacturer of oseltamivir.

In a Cochrane review on this topic, Jefferson et al [2] excluded 8 of the 10 studies in the Kaiser paper [1]. Without these 8 studies, they estimated that oseltamivir reduced the risk of influenza-associated complications (including upper respiratory complications that may not have required antibiotics) by 45%. Because the 95% confidence interval included 1, they concluded that there was no evidence of a benefit of oseltamivir. Several commentaries on this finding were published [3–7].

After the appearance of these articles, Roche asked us to perform an independent data analysis. We agreed to do so because the question is of considerable public health importance,

particularly in the context of a recent influenza pandemic. The agreement specified that we receive full access to efficacy and safety data from the 10 trials (we later requested data from additional trials), assistance from Roche statisticians in answering data-related questions, and complete freedom to publish any results. Neither we nor our institution received any funding for this work from Roche.

## METHODS

Besides the 10 trials in Kaiser et al [1], we identified another placebo-controlled, double-blind, randomized trial (WV16277) that collected data on antibiotic-treated LRTCs and that had been funded by Roche. An additional Roche-funded trial in Japan [8] did not appear to have collected data on antibiotic-treated LRTCs in a format compatible with this analysis.

The 11 trials in our analysis (see Supplementary Materials) included adults and adolescents with flu symptoms during the 1997–2001 influenza seasons. Patients were eligible if they presented within 36 hours of symptom onset and had fever (temperature  $\geq 37.8^{\circ}\text{C}$  if aged  $< 65$  y;  $\geq 37.5^{\circ}\text{C}$  if aged  $\geq 65$  y) plus at least 1 respiratory symptom (cough, sore throat, or coryza) and 1 constitutional symptom (headache, myalgia, chills/sweats, or fatigue). Patients were randomized to receive oseltamivir (75 mg twice daily) or placebo for 5 days.

The primary endpoint of our analysis was any lower respiratory tract complication (LRTC) treated with antibiotics. LRTC was not the primary or secondary endpoint in the original trials, but was reconstructed retrospectively from the database. We focused on LRTCs treated with antibiotics, rather than all LRTCs, because the former is a better surrogate of clinically relevant conditions. Antibiotic prescriptions were systematically recorded in the original trials. Our analyses excluded participants taking antibiotics at baseline. We also studied the following endpoints: gastrointestinal disorders (nausea, vomiting, diarrhea), neuropsychiatric disorders (other than headache), and headache.

Our analytic approach differed from that in Kaiser et al [1] in 3 ways.

First, we computed study-specific risk ratios of LRTC treated with antibiotics within the first 24 days of follow-up for oseltamivir versus placebo, and then we pooled the study-specific risk ratios using meta-analysis techniques. We used fixed-effect estimates when the *P* value for heterogeneity of a bootstrap *Q* statistic [9] was  $> .10$ ; otherwise, we used random effects. Kaiser et al [1] pooled the individual-level data from the studies, which may lead to confounding because both the distribution of risk

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factors and the probability of assignment to oseltamivir varied across studies.

Second, we included endpoints diagnosed during the first 2 days after randomization. These events were excluded by Kaiser et al [1] because they hypothesized that oseltamivir could have no effect during the first 2 days. Although reasonable, this approach deviates from the intention-to-treat principle used in many randomized trials, in which investigators refrain from making assumptions about the timing of effects and thus include all events after randomization in the analysis.

Third, Kaiser et al [1] excluded patients who deviated from protocol (eg, did not take the assigned treatment), and included patients who withdrew from the study only up to the withdrawal date. A true intention-to-treat analysis would include the complete follow-up of all randomized patients. We explored the sensitivity of the estimates to these exclusions.

Finally, we conducted subset analyses by influenza infection status, for comparability with the meta-analysis by Jefferson et al [2] and the subset analysis by Kaiser et al [1]. To do so, we had to pool individual-level data of small studies with zero cells. Other subset analyses could not be conducted because of insufficient sample sizes in several of the trials.

## RESULTS

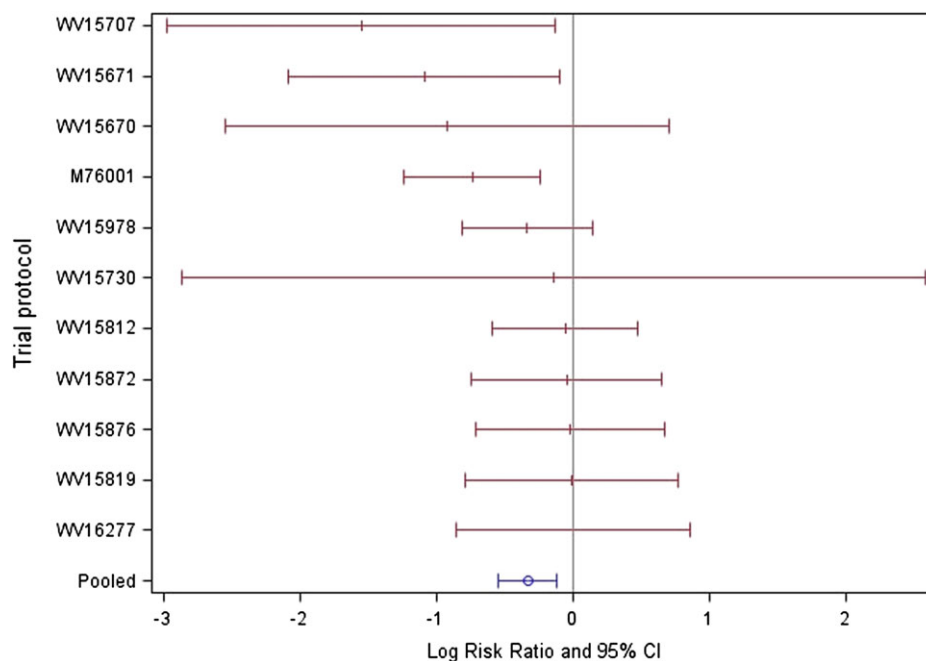
The analysis included 3908 patients: 2188 in the oseltamivir arms and 1720 in the placebo arms. 291 patients (130 oseltamivir, 161 placebo) had an LRTC treated with antibiotics within the first 24 days of follow-up; 28 cases (21.5%) occurred for oseltamivir and

20 (12.4%) for placebo in the first 2 days. The meta-analytic risk ratio of LRTC treated with antibiotics was .72 (95% confidence interval [CI], .58–.89; *P* value for heterogeneity = .30) for oseltamivir versus placebo (see Figure 1). Had we pooled individual-level data rather than meta-analyzed the study-specific risk ratios, the risk ratio would have been .63 (95% CI, .51–.79). Had we further ignored events during the first 2 days of follow-up, the risk ratio would have been .57 (95% CI, .44–.73).

The risk ratio (95% CI; *P* value for heterogeneity) was 1.46 (1.05–2.02; .06) for nausea, 1.55 (1.14–2.12; .01) for vomiting, .83 (.66–1.04; .44) for diarrhea, 1.47 (1.05–2.04; .36) for headache, and 1.02 (.72–1.44; .83) for other neuropsychiatric disorders.

Of the 3908 patients, 2570 were infected with influenza at baseline (1429 oseltamivir, 1141 placebo). Of these 2570 patients, 201 (79 oseltamivir, 122 placebo) had an LRTC treated with antibiotics within the first 24 days of follow-up; 16 cases (20.3%) for oseltamivir and 15 (12.3%) for placebo occurred in the first 2 days. Among influenza-infected patients, the risk ratio of LRTC treated with antibiotics was .63 (95% CI, .48, .82; *P* value for heterogeneity = .18) for oseltamivir versus placebo. A pooled analysis would have estimated a risk ratio of .52 (95% CI, .39–.68). If we had further ignored events during the first 2 days of follow-up, the risk ratio would have been .47 (95% CI, .35–.64), similar to the findings of Kaiser et al [1]. An analysis of the 10 studies reported by Kaiser et al [1] reproduced their finding precisely.

Of the remaining 1338 patients (759 oseltamivir, 579 placebo) who were not infected with influenza, 90 (51 oseltamivir, 39 placebo) had an LRTC treated with antibiotics within the first 24



**Figure 1.** Oseltamivir and the risk of lower respiratory tract complications requiring antibiotics.

days of follow-up. The risk ratio of LRTC treated with antibiotics was 1.06 (95% CI, .71–1.58; *P* value for heterogeneity = .97) for oseltamivir versus placebo.

Kaiser et al [1] excluded 24 patients (14 oseltamivir, 10 placebo) who were randomized. We repeated the analyses under a scenario that would be unrealistically unfavorable to oseltamivir: half of the oseltamivir patients but no placebo patients developed the outcome. The risk ratio was .75 (95% CI, .60, .93; *P* value for heterogeneity = .45).

A total of 159 patients (96 oseltamivir, 63 placebo) withdrew before the endpoint or 24 days of follow-up. We repeated the analyses under an unrealistic scenario that was unfavorable to oseltamivir: among those who withdrew, a quarter of oseltamivir patients but no placebo patients developed the outcome. The risk ratio was .82 (95% CI, .67–1.01; *P* value for heterogeneity = .50).

For LRTC in general, the risk ratio (95% CI; *P* value for heterogeneity) for oseltamivir versus placebo was .76 (.62–.93; .19) in all patients, .71 (.56–.90; .35) in influenza-infected patients, and .96 (.66–1.39; .95) in non-influenza-infected patients.

## CONCLUSION

Our reanalysis confirms that oseltamivir reduces the risk of LRTC treated with antibiotics among patients with flu symptoms or with confirmed influenza. The 24-day risk reduction was about 28% overall and 37% in patients with influenza infection. No reduction was observed in patients without influenza. The effect estimates changed little even under rigorous sensitivity analyses. We also confirmed previous reports of increased risk of nausea and vomiting [2, 10], but found no evidence of increased risk of neuropsychiatric disorders, except for headache, among those assigned to oseltamivir.

As for any meta-analysis, the quality of our estimates depends on the quality of the individual studies. Of the 11 trials included in the meta-analysis, only 2 have been published in peer-reviewed journals [11, 12]. The other 9 were either unpublished or published only in abstract form until their findings were reported by Kaiser et al. Jefferson et al considered the unpublished trials analyzed by Kaiser et al as “inaccessible to proper scrutiny” and excluded them from their Cochrane meta-analysis. However, the unpublished trials are no more favorable to oseltamivir than the published ones. Using only the 2 published trials, the reduction in the 24-day risk of LRTC treated with antibiotics is 65% (risk ratio, .35; 95% CI, .15–.82) in the oseltamivir arms.

Our reanalysis has at least 2 limitations. First, it was not possible to assess the potential benefit for high-risk participants who are hospitalized [13], because the sample size of most studies was too small to consider hospitalization as an outcome. Second, the data in these studies were collected in an era without viral resistance to oseltamivir. The effectiveness of oseltamivir may be different now.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online ([http://www.oxfordjournals.org/our\\_journals/cid/](http://www.oxfordjournals.org/our_journals/cid/)). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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